DECLARATION UNDER RULE 132		
	Application #	10/587,899
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	First Inventor	SCHWARTZ Jean-Charles
	Art Unit	1614
	Examiner	Spivack, Phyllis G.
	Docket #	P08977US00/BAS

Commissioner for Patents
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S I R:

I, Jeanne-Marie Lecomte, residing in Paris (75003), 30 rue des Francs-Bourgeois, France, declare and say as:

1. I am a French citizen.

2. I am Ph.D in Sciences, author of more than 120 scientific publications in different fields, including clinical pharmacology and clinical trials, and presently Chairman of Bioprojet.

3. I am aware that the instant claims are being rejected under 35 USC103(a) as being unpatentable over Cojocaru et al., in view of Cubbedu et al. and Boige et al..

4. Nevertheless, none of the above references suggests the synergy which we surprisingly found when combining dexecadotril and ondansetron.

5. Diarrhoea generally involves the two following components:
   - loss of water and salts, and
   - acceleration of the intestinal transit.

Loss of water and salts leads potentially to dehydration, one of the main life-threatening complications in diarrhoea.

6. Racecadotril and dexecadotril exhibit a strong anti-secretory effect in that they substantially facilitate the reabsorption of water and salts from the intestinal lumen and thereby inhibit the associated loss of water and salts in diarrheic patients. However, these agents may induce an acceleration of the intestinal transit. This acceleration tends to limit the antisecretory effects of these drugs (inasmuch as the reabsorption process has not time enough to fully develop in the intestinal lumen) and it is also a possible undesirable side effect of racecadotril.

It was shown in the previously filed declaration that coadministration of racecadotril with granisetron surprisingly suppresses this side effect of racecadotril and hence potentiates the anti-diarrhoeal activity of racecadotril in mice.

This result shows that the side effect of racecadotril may be prevented by granisetron. There was no suggestion that granisetron would slow down the increase of intestinal transit caused by racecadotril. This combination is thus unobvious.

7. Further to the current Examiner's objection, Boige merely describes the administration of ondansetron to treat emesis and the administration of racecadotril to treat diarrhoea. Boige does not suggest combining these substances to suppress the side effect of racecadotril and thereby potentiate the antidiarrheal effect of the latter.

8. Further, it is well-known to the clinician that ondansetron is an anti-emetic agent (i.e. inhibiting nausea/vomiting) and does not possess anti-diarrhoeic activity. Rather, it was found as increasing the occurrence of diarrhoeal episodes.

This fact is ascertained by Cubbedu, which relates to the administration of ondansetron for the treatment of emesis associated with acute gastroenteritis. Cubbedu shows that the administration of ondansetron increases the number of diarrhoeal episodes, compared to a placebo (see Table 3, p.189 of Cubbedu):

Number of diarrhoeal episodes	Ondansetron (0.3 mg/kg – 12 patients)	Placebo (12 patients)
0-4	4 (33%)	8 (67%)
5-9	1 (8%)	4 (33%)
10-14	3 (25%)	0
> 14	4 (33%)	0

Number of patients experiencing diarrhoeal episodes during 0-24 h following treatment

In particular, Cubbedu concludes (p.187, last paragraph): "*compared with placebo significantly more episodes of diarrhoea were reported in the ondansetron (P=0,013) group*".

9. We surprisingly showed that coadministration of ondansetron with dexecadotril suppresses the increase in the intestinal transit induced by dexecadotril while reducing the number of diarrheic stools and the duration of diarrhoea.

The following study was directed to the administration of dexecadotril 100 mg tablets, and dexecadotril 100 mg combined with ondansetron tablets (1 mg, 3 mg, or 6 mg) in order to treat diarrhoea in adult outpatients. The study was performed on 213 patients in 4 groups, as follows:

Group name	DX	DX+01	DX+03	DX+06
Treatment	dexecadotril 100 mg	dexecadotril 100 mg ondansetron 1 mg	dexecadotril 100 mg ondansetron 3 mg	dexecadotril 100 mg ondansetron 6 mg
Number of patients	54	50	54	55

Composition of the 4 patient groups for the clinical study

The patients of each group were to take 1 tablet 3 times a day at the beginning of each meal until recovery.

9.1. The following data illustrate the effect of dexecadotril alone or together with ondansetron on the mean number of diarrheic stools (NDS).

	DX	DX+01	DX+03	DX+06
Mean NDS	11.5 ± 9	8.5 ± 8.8	8.1 ± 7.2	8.2 ± 12.9

Mean number of diarrheic stools in patients following treatment

The above results show that coadministration of dexecadotril with ondansetron decreases the number of diarrheic stools more significantly than dexecadotril alone.

9.2. The following data illustrate the effect of dexecadotril alone or together with ondansetron on the duration of diarrhoea.

	DX	DX+01	DX+03	DX+06
Mean diarrhoea duration (hour)	41.2 ± 29.9	31 ± 26.2	34.4 ± 22.5	25.2 ± 24.7

Mean diarrhoea duration in patients following treatment

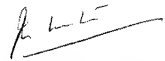
The above results show that coadministration of dexecadotril with ondansetron reduces the duration of diarrhoea more significantly than dexecadotril alone.

10. Given that ondansetron does not possess anti-diarrhoeal activity and even increases diarrhoea, the above potentiation of the anti-diarrhoeal activity of dexecadotril when combined with ondansetron illustrates a synergy between these two compounds. These results are surprising and could not have been expected by the skilled person.

The combination of dexecadotril or racecadotril with ondansetron or granisetron thus involves an inventive step.

11. The undersigned declares further that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 24th day of May 2011



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